43 Alterations in septohippocampal cholinergic receptors and related behavior after early exposure to nicotine.

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In previous investigations we established a mouse model for the study of drug neuroteratogenicity; phenobarbital was then selected as the model drug. The studies ascertained alterations in the septohippocampal cholinergic pathways related to prenatal phenobarbital-induced deficits in hippocampal-dependent behaviors. There were increases in the B_{max} of muscarinic receptors and their second messenger, inositol phosphate, after early exposure to phenobarbital, while almost no presynaptic cholinergic alterations were found. Concomitant deficits were demonstrated in the hippocampus-related eight-arm maze behavior. Consequently, the behavioral deficits could be reversed by transplantation of cholinergic cells to the impaired hippocampus. Therefore, it is now becoming feasible to apply this model on the more commonly abused nicotine. Mice were exposed to nicotine prenatally by injecting the mother 1.5 mg/kg nicotine s.c. once daily on gestation days 9-18 (PreN mice), or neonatally, by daily s.c. injections of 1.5 mg/kg nicotine to the pups on days 2 to 21 (NeoN mice). On age 50 days, the mice were tested in the eight-arm maze and their hippocampi were assayed for muscarinic receptor binding using ^{3}H-QNB as a ligand. PreN and NeoN mice made 28% more errors in the maze than control before reaching criterion ($p < 0.01$). Hippocampal muscarinic receptors B_{max} of controls was 1.12±0.21 pmol/mg protein (Mean±SEM). The score for PreN was 1.77±0.02 and for NeoN mice 2.00±0.06; increases of 58% and 79% from control respectively ($p < 0.01$). On the other hand, K_D was unaffected by early nicotine exposure. Whether alterations can be demonstrated in the subsequent steps of the postsynaptic cholinergic transmission and, similarly to the phenobarbital model, the biochemical and behavioral deficits can be reversed by neural grafting, remains the subject of our current investigations.